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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,083	07/13/2001	Timothy I. O'Brien	D6223CIP/C/D	4623

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,083	O'BRIEN, TIMOTHY I.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01 September 2006 has been entered.

2. Claims 1-25, 27-29 and 32-39 are cancelled.

Claims 26 and 31 have been amended.

3. Claims 26 and 30-31 are pending and under examination.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Rejections.

Withdrawn Rejections

6. The rejection of claims 30-31 under 35 U.S.C. 112, first paragraph (item no. 4 of the final Office Action), because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims is withdrawn in view of the amendments to the claims.

Response to Arguments

7. Claims 26 and 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing activated T cells directed towards human stratum corneum chymotrytic enzyme (SCCE) comprising exposing isolated dendritic cells to the SCCE peptide consisting of SEQ ID NO:32 and exposing isolated dendritic cells to the mature human SCCE polypeptide encoded by SEQ ID NO:30 (i.e., lacking the signal peptide and propolypeptide) thereby producing activated dendritic cells and exposing said dendritic cells to isolated T cells wherein said activated dendritic cells present the SCCE peptide to said isolated T cells, thereby producing activated T cells directed towards said human SCCE, does not reasonably provide enablement for all embodiments embraced by the claims is maintained and made again.

The response filed 9/1/2006 has been fully considered, but is deemed not to be persuasive. The response states that as presently amended, claim 26 does not encompass any other peptides other than those recited in the claim and claim 31 is amended to include cancers where the stratum corneum chymotrytic enzyme is amplified as described in the Declaration under 37 CFR 1.132 by Dr. Timothy J. O'Brien. Applicant again refers to the previously submitted a Declaration under 37 CFR 1.132 by Dr. Timothy J. O'Brien (filed 2/19/2003) which established that SCCE peptide 5-13 (SEQ ID NO:33) and SCCE peptide 123-131 (SEQ ID NO:32) induce CD8+ CTL responses in vitro. In response to the cited art of Hansson et al, Applicant previously submitted a second

declaration under 37 CFR 1.132 (filed 1/23/2006), which provides evidence that the SCCE peptide 5-13 (SEQ ID NO:33) of the signal peptide of SCCE effectively generates CTLs that lyse ovarian cancer cells when the cells were not pulsed initially with the SCCE peptide of SEQ ID NO:33 providing evidence that the SCCE 5-13 peptide of the signal peptide is naturally expressed, processed and presented by ovarian tumor cells. The Declarations under 37 CFR 1.132 filed 2/19/2003, 1/23/2006 and 9/1/2006 are insufficient to overcome the rejection of claims 26, 30 and 31 based upon insufficiency of the disclosure under 35 U.S.C. 112, first paragraph as set forth in the last Office action because the showing is not commensurate in scope with the claims. Again, while the Declarations submit evidence that SCCE peptide 5-13 (SEQ ID NO:33) and SCCE peptide 123-131 (SEQ ID NO:32) induce CD8+ CTL responses in vitro, the claims still encompass.SCCE peptides other than SEQ ID Nos:32 and 33 that do not contain amino acids 5-13 or 123-131 of SCCE as well as the treatment of just any disorder, particularly ovarian, prostate, breast and colon cancer as presently recited in claim 31. Further, the claims still encompass SCCE dendritic cell immunotherapy in cancer patients (i.e., "reintroduced into said individual subsequent to exposure") while the showings in the Declarations are limited to in vitro evidence and nucleic acid expression rather than polypeptide expression. Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. In fact, evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. For example, Fu et

al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Further, Powell et al (Pharmacogenetics, 1998, Vol. 8, pp. 411-421, abstract) teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133, abstract) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. Lewin B. (Genes VI, 1997, CH. 29, pp. 847-848) acknowledges that control of gene expression can occur at multiple stages, and that production of RNA *cannot inevitably* be equated with production of protein (see page 847, right column). These references demonstrate that the analysis of levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression and one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification.

Applicant also submits the art of Cho et al, Kurokawa et al, Santin et al, Wurtzen et al, Wong et al, Noriaki et al, Higuchi et al, Ritchie et al, Li et al and Van Gulck et al in support of the assertion that dendritic cell based therapy to treat malignant conditions were known and enabling as of the filing date of the instant application and the art of dendritic cell immunotherapy was not unpredictable as stated by the examiner. This has been fully considered but is

not found persuasive. With the exception of the art of Noriaki et al, Higuchi et al and Van Gulck et al, the references submitted by applicant are limited to the in vitro stimulation of dendritic cells and provide a starting point for further experimentation into their use for patient specific immunotherapy. Further, the art of Higuchi et al and Van Gulck et al were published after the filing date of the present application. With respect to the art of Noriaki et al, Higuchi et al and Van Gulck et al, which does show efficacy using dendritic cell immunotherapy in patients, as discussed supra, the claims still encompass SCCE peptides other than SEQ ID Nos:32 and 33 that do not contain amino acids 5-13 or 123-131 of SCCE and there is no evidence that the SCCE signal peptide (i.e., comprising amino acids 5-13) is part of the mature SCCE protein expressed in cancer patients such that SCCE activated T cells targeting this sequence effectively inhibit tumor growth in a patient. Again, the examiner acknowledges that a large body of art exists as it pertains to dendritic cell adaptive immunotherapy, however, despite the large body of art that exists as evidenced by the references submitted by applicant, Cranmer et al and Soruri et al cited by the examiner are evidence that all of the parameters for the clinical application of dendritic cells in the treatment of cancer have not been standardized and are not yet predictable. It is reiterated that Cranmer et al (Cancer Immunology and Immunotherapy, 53(4):275-306, April 2004, cited on PTO-892 mailed 4/4/2006) teaches that most clinical trials to date have not yielded data from which firm conclusions can be drawn and optimal parameters in humans remain to be established (see abstract). At page 277, left column, Cranmer et al teach that many routes of

vaccination have been utilized, but there is limited information regarding the optimal route, optimal dose has not been determined, maximal cell dose is limited, at present, by the ability to culture the cells in large numbers, there is no standard or optimal schedule for dendritic cell administration, the use of maintenance vaccinations, and the use of revaccination after failure have not been addressed (see also pg. 303, left column). Further, Soruri et al (The International Journal of Biochemistry and Cell Biology, 37(2):241-245, February 2005, cited on PTO-892 mailed 4/4/2006) teach that despite the wide use monocyte-derived dendritic cells (MoDC) for experimental and clinical immunotherapy, unequivocal proof for clinical efficiency of MoDC-based anti-tumor vaccinations is still missing and MoDC may not represent the equivalent of migratory dendritic cells in vivo limiting their use as magic bullets in tumor immunotherapy (see abstract). More importantly, Applicant has not provided any guidance or direction regarding any of the above parameters for reintroducing SCCE activated dendritic cells in cancer patients and the instant specification does not provide any in vitro data regarding the efficacy of computer predicted motifs for HLA class I molecules to induce SCCE-specific CTL. The selection of the SCCE peptides of SEQ ID Nos:31-36, 80, 86 and 99 using a computer program and the showing that SEQ ID Nos:32 and 33 are effective at inducing specific CD8+ CTL responses in vitro is insufficient to support the enablement of the full scope of the claims because the specification does not provide any guidance as it pertains to different dendritic cell sources, different precursor cell mobilization methods, different dendritic cell culture methods and different

cytokine mixtures to induce their development, different durations, concentrations and other parameters in the antigen exposure process, different routes, schedules and cell doses for immunization, non-standardized means of assessing induced immune responses and incomplete description of clinical responses. Applicant essentially leaves this significant portion of their invention to those skilled in the art to begin to discover for themselves how to effectively practice the claimed method, which is not predictable or standardized in the current state of the art and such experimentation is labor- and resource-intensive according to Cranmer et al (see abstract). The evidence of record does not show that a skilled artisan would have been able to carry out the steps required to practice the full scope of claims, which encompasses reintroducing activated dendritic cells into an individual/patient for producing activated T cells in vivo toward SCCE that effectively treats any disorder, in particular, ovarian, prostate, breast and colon cancer, without undue experimentation.

Additionally, as it pertains to applicants' reliance on computer predicted SCCE motifs for HLA class I molecules to induce SCCE-specific CTL, the art of Wang et al (US Patent 5,840,839, of record) is evidence that finding a peptide that binds to an MHC molecule and stimulates an immune response is not a trivial matter. The '839 patent at columns 19-20 and table 1 teach that the various candidate T cell epitopes selected based on theoretical binding motifs (i.e., computer predicted) of one class of MHC molecule, i.e., HLA-A31 do not work when they are experimentally tested as shown in Table 1. Further, the art of Geysen (US Patent 5,539,084, of record) demonstrates that even for peptides

of similar size derived from the same "parent" polypeptide, not all will be capable of interacting with T-cells (column 2, lines 5-9 and Figure 6), thus demonstrating the degree of uncertainty in the art for predicting which subsets or portions of a larger polypeptide will be capable of interacting with or stimulating T-cells. While Applicant is not claiming broadly, i.e., applicant is claiming the specifically recited SCCE peptides, Applicant has not provided any objective evidence demonstrating that the claimed method of producing activated T cells against the theoretical SCCE peptides of SEQ ID Nos:31, 34, 35, 36, 80, 86 and 99 effectively stimulate T cells that induce peptide-specific cytotoxicity in ovarian, prostate, breast and colon cancer patients.

In view of the lack of predictability of the art to which the invention pertains as evidenced by Cranmer et al, Soruri et al, Wang et al and Geysen et al, the lack of established clinical protocols for effective dendritic cell therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods of dendritic cell immunotherapy to treat ovarian and prostate cancer patients in particular, commensurate in scope with the claimed invention.

For these reasons and those already of record the rejection of claims 26 and 30-31 for lack of enablement is maintained.

New Grounds of Rejections

8. Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing new matter. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 9/1/2006 has introduced NEW MATTER into the claims. As presently amended claim 31 is drawn to the claimed immunotherapeutic method of wherein the individual has breast or colon cancer. The response did not point out where support for presently amended claim 31, i.e., wherein the individual has breast or colon cancer, could be found in the originally filed disclosure. Although the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims, when filing an amendment an applicant should show support in the original disclosure for new or amended claims. See MPEP 714.02 and 2163.06 ("Applicant should therefore specifically point out the support for any amendments made to the disclosure."). As presently amended, claim 31 now recites limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in presently amended claim 31, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112.

Applicant is required to provide sufficient written support for the limitations recited in presently amended claim 31 in the specification or claims, as-filed, or remove these limitations from the claims in response to this Office Action.

Conclusions

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827